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Associations of Trimester-Specific Exposure to Bisphenols with Size at Birth: A Chinese Prenatal Cohort Study

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Background: Bisphenol A (BPA) is an endocrine disruptor that affects fetal growth in experimental studies. Bisphenol F (BPF) and bisphenol S (BPS), which have been substituted for BPA in some consumer products, have also shown endocrine-disrupting effects in experimental models. However, the effects of BPF and BPS on fetal growth in humans are unknown.

Objectives: Our goal was to investigate trimester-specific associations of urinary concentrations of BPA, BPF, and BPS with size at birth.

Methods: The present study included 845 pregnant women from Wuhan, China (2013–2015), who provided one urine sample in each of the first, second, and third trimesters. Linear regressions with generalized estimating equations were applied to estimate trimester-specific associations of urinary bisphenol concentrations with birth weight, birth length, and ponderal index. Linear mixed-effects models were used to identify potential critical windows of susceptibility to bisphenols by comparing the exposure patterns of newborns in the 10th percentile of each birth anthropometric measurement to that of those in the 90th percentile.

Results: Medians (25th–75th percentiles) of urinary concentrations of BPA, BPF, and BPS were 1.40 (0.19–3.85), 0.65 (0.34–1.39), and 0.38 (0.13–1.11) ng/mL, respectively. Urinary BPA concentrations in different trimesters were inversely, but not significantly, associated with birth weight and ponderal index. Urinary concentrations of BPF and BPS during some trimesters were associated with significantly lower birth weight, birth length, or ponderal index, with significant trend p-values ($p_{trend} < 0.05$) across quartiles of BPF and BPS concentrations. The observed associations were unchanged after additionally adjusting for other bisphenols. In addition, newborns in the 10th percentile of each birth anthropometry measure had higher BPF and BPS exposures during pregnancy than newborns in the 90th percentile of each outcome.

Conclusions: Prenatal exposure to BPF and BPS was inversely associated with size at birth in this cohort. Replication in other populations is needed. https://doi.org/10.1289/EHP4664

Introduction

Bisphenol A (BPA), a synthetic chemical used in the manufacture of polycarbonate plastics and epoxy resins, can be found in a variety of consumer products, including some food and beverage cans, plastic bottles, receipts, and medical equipment (Pergialiotis et al. 2018; Rochester and Bolden 2015). BPA is an endocrine-disrupting chemical that acts as a physiological receptor in a variety of pathways (Richter et al. 2007). Fetuses are directly exposed to BPA because it crosses the placenta (Balakrishnan et al. 2010; Peretz et al. 2014). Several human studies have linked higher levels of BPA exposure during pregnancy to reduced size at birth, as well as to increased risk of adverse birth outcomes (Cantonwine et al. 2015; Huo et al. 2015; Miao et al. 2011; Snijder et al. 2013), whereas other studies did not report such associations (Casas et al. 2016; Ferguson et al. 2016; Lee et al. 2014; Philippat et al. 2012; Smarr et al. 2015).

In consideration of the toxicity of BPA and consumer concern, manufacturers have begun to remove BPA from their products, with gradual transitions to using bisphenol analogs. As a result, bisphenol F (BPF) and bisphenol S (BPS) have been widely used in manufacturing a variety of BPA-free products (Bittner et al. 2014; Rochester and Bolden 2015). In recent studies, BPF and BPS were detected in some personal care products, receipt paper, and food in several countries, including the United States, China, Japan, and Korea (Liao et al. 2012b; Liao and Kannan 2014a, 2014b). Furthermore, BPF and BPS have also been found in urine samples of populations from the United States, China, and several other countries from Asia and Europe at levels comparable to those of BPA (Andrianou et al. 2016; Liao et al. 2012a; Liu et al. 2017; Ye et al. 2015; Zhang et al. 2016).

Prenatal exposure to BPA may affect fetal growth through multiple hormone-mediated mechanisms because of its properties

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of mimicking estrogen, inhibiting androgen production, altering thyroid signaling, and causing oxidative stress (Peretz et al. 2014; Tomza-Marciniak et al. 2018). In addition, exposure to BPA at levels consistent with plasma concentrations in pregnant women may affect placental functions by inducing the apoptosis of primary human cytotrophoblast cells through tumor necrosis factor-α (Benachour and Aris 2009). A systematic review of *in vitro* and experimental studies concluded that BPF and BPS might have endocrine-disrupting effects similar to BPA (Rochester and Bolden 2015). BPF and BPS have also been shown to affect zebrafish in a manner similar to the effects of BPA at low (environmentally relevant) exposure levels (Kinch et al. 2015; Qiu et al. 2016). However, evidence from epidemiological studies is scarce. To our knowledge, only two recent studies have investigated prenatal exposure to BPS in association with birth outcomes, with one reporting an inverse association between detectable (vs. nondetected) maternal urinary BPS concentrations and birth weight (Ferguson et al. 2018) and the other reporting a significant overall association with longer pregnancy duration but not with birth weight or length (Wan et al. 2018). To our knowledge, no epidemiological studies have investigated the effect of prenatal exposure to BPF on fetal growth.

In this longitudinal prenatal cohort study in Wuhan, China, we estimated trimester-specific associations of urinary concentrations of BPA, BPF, and BPS with birth weight, birth length, and ponderal index in 845 pregnant women who provided urine samples at three time points during pregnancy. We further investigated whether associations differed by trimester, which would be indicative of windows of heightened susceptibility to bisphenol exposures during pregnancy.

Methods

Study Participants

The present study was carried out based on an ongoing longitudinal prenatal cohort study in Wuhan, Hubei Province, China. Participants were recruited at Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), the municipal health center for women and children in Wuhan (Wu et al. 2019). Pregnant women who received their first prenatal care visits before 16 weeks of gestation were eligible. Women were enrolled in the prenatal cohort study if they *a*) were residents of Wuhan; *b*) comprehended the Chinese language; *c*) agreed to have in-person interviews, take ultrasound examinations, and provide blood and urine samples at different governmental recommended prenatal care visits; *d*) were willing to give birth at the study hospital; and *e*) provided signed informed consent. The present study included 856 women, sampled between October 2013 and October 2015, who satisfied the inclusion criteria, gave birth to live singletons without birth defects, and provided three urine samples, one in each of the three trimesters. Of these, 845 women were retained after additionally excluding women who used tobacco ($n = 5$) or consumed alcohol ($n = 4$) before or during pregnancy, as well as women with missing values in covariates ($n = 2$). The study protocol was reviewed and approved by the ethics committees of Tongji Medical College, Huazhong University of Science and Technology, and of the Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital).

Urine Collection and Analysis

Urine samples of pregnant women were obtained at governmental recommended prenatal care visits in the first [mean ± standard deviation (SD) = 13.0 ± 1.1 weeks, the first prenatal care visit; range: 10–16 weeks], second (mean ± SD = 23.6 ± 3.2 weeks; range: 19–27 weeks), and third (mean ± SD = 36.0 ± 3.4 weeks; range: 32–41 weeks) trimesters and were stored at −20°C in polypropylene cups prior to analyses. All women included in the present study provided one urine sample in each trimester. Moreover, 688 (81.4%) of the women provided their first-trimester urine samples at or prior to 13 weeks of gestation.

The methods for determining urinary bisphenol concentrations have been described elsewhere (Zhao et al. 2018). Briefly, a 1-mL urine sample was withdrawn from samples after being thawed at room temperature (about 25°C). After adding internal standards of bisphenols, working solutions were incubated overnight for digestion and were then extracted. Before analyzing, the upper organic layers were collected and evaporated under nitrogen gas flow and then reconstituted. Finally, urinary concentrations of BPA, BPF, and BPS were simultaneously measured by an ultra-high performance liquid chromatograph (Dionex) coupled with a triple quadrupole mass spectrometer (Thermo Scientific). Each analytical batch contained all three urine samples of one woman collected at different time periods, as well as blanks and quality control samples. The limits of detection (LODs) were 0.04 ng/mL for BPA, 0.02 ng/mL for BPF, and 0.04 ng/mL for BPS. The linear ranges of the calibration curves ranged from 1.00 to 50 ng/mL for BPA and BPS and ranged from 0.50 to 50 ng/mL for BPF. All calibration curves showed excellent linearity ($R^2 \geq 0.9901$). Intra- and interday precisions were lower than 7.7% and 10.1% for all three bisphenols.

Specific gravity (SG) for each urine sample was measured at room temperature by a hand-held digital refractometer (Atago PAL-3; Atago), which was calibrated before each measure using deionized water.

Birth Anthropometry

Information on birth weight (in grams) and birth length (in centimeters) was retrieved from medical records. Ponderal index (in kilograms per cubic meter) was calculated as 1,000 times birth weight (in grams) divided by the cube of birth length (in meters). A low ponderal index indicates an asymmetrical intrauterine growth retardation (Landmann et al. 2006). Gestational age at delivery was calculated as days between the date of delivery and the first day of the last menstrual period (LMP), which was reported by the participants and also corrected by obstetricians according to the first-trimester ultrasound measures based on clinical criteria. The information on both reported and corrected gestational ages at delivery was retrieved from medical records. For women who reported an accurate date of the LMP (i.e., the difference between the reported and corrected date of the LMP was less than 7 d), a reported gestational age was used; otherwise, an ultrasound corrected gestational age was used.

Gestational age-adjusted percentiles of birth weight, birth length, and ponderal index were calculated based on the gestational age-adjusted standard deviation scores (SD-scores) for each birth anthropometry. These SD-scores were generated based on all available data (Hu et al. 2018) using the *GAMLSS* package (version 4.3-7) in the R software (version 3.3.2; R Development Core Team). The assumption was that the distributions of these parameters depend only on gestational age. We first performed Box-Cox transformations to normalize these parameters (Rigby and Stasinopoulos 2005). Then, we modeled each parameter as a function of gestational age in days using a cubic spline according to different distribution families (BCPEo, BCCGo, and BCTo) provided by the *GAMLSS* package. Finally, the best fitting model for each birth anthropometry with a specific distribution was selected based on the Akaike's information criteria and was then used to generate the gestational age-adjusted SD-score for each birth anthropometry.

Covariates

In-person interviews were conducted by trained nurses at the first prenatal care visits using standardized and structured questionnaires to collect information on maternal age, socioeconomic status (e.g., education and annual household income), perinatal lifestyle before and during pregnancy (e.g., tobacco smoking, passive smoking, and alcohol consumption), folic acid supplement use during pregnancy, and anthropometric data (maternal height and prepregnancy weight and paternal height and weight). Passive smoking was defined as being exposed to secondhand smoke during pregnancy from either family members (at home) or colleagues (at work). Maternal prepregnancy body mass index (BMI) and paternal BMI were calculated as weight (in kilograms) divided by height in meters squared. Clinical information (e.g., parity, hypertensive disorders of pregnancy, gestational diabetes mellitus, anemia, and infant sex) was retrieved from medical records, as diagnosed by experienced obstetricians at prenatal care visits as routine clinical care in the study hospital.

Statistical Analysis

Urinary concentrations (in nanograms per milliliter) of BPA, BPF, and BPS below the levels of LODs were replaced by the LODs divided by the square root of 2. For each bisphenol, we standardized its concentrations for urine dilution using the following equation: $P_i = P[(1.011–1)/(SG–1)]$, where P represents the unadjusted concentrations, 1.011 is the median SG of all measurements, and SG represents the specific gravity of individual urine samples (Duty et al. 2005). Average concentrations of each bisphenol across the three trimesters were also calculated. SG-standardized bisphenol concentrations were transformed by natural logarithm to reduce the influence of outliers. Pearson correlation coefficients of urinary concentrations of BPA, BPF, and BPS in each trimester were calculated for within-trimester comparisons.

Intraclass correlation coefficients (ICCs) and 95% confidence intervals (CIs) of urinary SG and urinary bisphenol concentrations were estimated using mixed-effects models in order to estimate their reproducibility. The ICC is the ratio of between-subject variance to total variance with a range from 0 (no reproducibility) to 1 (perfect reproducibility) (Rosner 2000). In addition, poor reproducibility was defined as an ICC <0.40, fair-to-good reproducibility as an ICC between 0.40 and 0.75; and excellent reproducibility as an ICC ≥ 0.75.

In order to estimate trimester-specific associations of urinary bisphenol concentrations with indicators of size at birth, we used a multiple informant model based on the repeated measures of urinary concentrations of BPA, BPF, and BPS (Sánchez et al. 2011). This multiple informant model treated urinary bisphenol concentrations at different time windows as informants and simultaneously estimated associations of each individual bisphenol concentrations with a given indicator of size at birth, and was conducted using linear regression with generalized estimating equations. In addition, this approach did not adjust for certain bisphenol concentrations in other time windows. Instead, it tested the null hypothesis that coefficients for certain bisphenol were equal at each visit; the p-value for this test, denoted as p_w, alludes to the interaction between exposure levels of bisphenols and timing of exposure (Sánchez et al. 2011). A $p_w < 0.05$ indicates that at least one association differed from the rest. We applied multiple informant models to estimate trimester-specific associations of urinary concentrations of BPA, BPF, and BPS in the first, second, and third trimesters with birth weight, birth length, and ponderal index. Original values of these birth anthropometric measurements were used in these multiple informant models. Regression coefficients (βs) and 95% CIs were estimated per interquartile range (IQR) increase (as continuous variables) and trimester-specific quartiles (with the lowest quartiles set as references) of urinary concentrations of each bisphenol. In order to test ordered relations across quartiles of urinary concentrations of BPA, BPF, and BPS, tests for linear trend (p_{trend}) were performed by modeling the median value of each quartile. Associations between average concentrations of each bisphenol across the three trimesters (per IQR increase and quartiles) and size at birth were also estimated using linear regression models.

In addition, we estimated exposure patterns for given outcome levels, using the methods of Sánchez et al. (2011), to evaluate which periods of pregnancy were more likely to be critical windows of susceptibility to bisphenols. Specifically, we used separate linear mixed-effects models for each bisphenol to compare urinary concentrations according to gestational age at measurement between newborns with low- versus high-gestational age-adjusted SD-scores (in the 10th percentile vs. in the 90th percentile, respectively) for birth weight, birth length, and ponderal index.

Regression models were adjusted for gestational age at delivery (continuous, in multiple informant models), maternal age at recruitment (continuous), parity (nulliparous/multiparous), maternal prepregnancy BMI (categorized using the Chinese standard: $<18.5/18.5–23.9/\geq 24.0\,kg/m^2$), folic acid supplementation during pregnancy (no/only in the first trimester/only in the second and third trimester/during the entire pregnancy), passive smoking during pregnancy (no/yes), education ($\leq 9/9–12/>12$ y), maternal and paternal height (continuous, in birth-length models), and infant sex (boys/girls). We also included urinary concentrations of BPA, BPF, and BPS in the same model in order to mutually adjust for each other.

We conducted a stratified analysis by infant sex (boys and girls) because we observed a sex-based difference in the association between prenatal exposure to BPA and birth weight risk in a previous study (Huo et al. 2015). Stratified analyses were also carried out based on maternal age at recruitment (by median age of 27 y), parity (by nulliparous and multiparous), and prepregnancy BMI [by underweight ($<18.5\,kg/m^2$), normal (18.5–$23.9\,kg/m^2$), and overweight and above ($\geq 24.0\,kg/m^2$) according to the Chinese standard]. In addition, p-values for interaction ($p_{interaction}$) were estimated as the p-values for the interaction terms of stratified variable and urinary concentrations of each bisphenol in order to test differences in associations of each strata. As a sensitivity analysis, models were additionally adjusted for hypertensive disorders of pregnancy (no/hypertension/preeclampsia), gestational diabetes mellitus (no/yes), and anemia (no/yes) in order to test for the potential impact of pregnancy complications. Other sensitivity analyses were conducted by replicating all regression models restricted to term deliveries or women without pregnancy complications (hypertensive disorders of pregnancy, gestational diabetes mellitus, or anemia).

All statistical analyses were performed using R (version 3.3.2; R Development Core Team) or SAS (version 9.4; SAS Institute Inc.). The statistical significance level was set to 0.05 for a two-tailed test.

Results

On average, the 845 women included in the present study were 27.9 ± 3.4 y of age. The study participants were predominantly nulliparous (85.9%) and well educated (78.9% had at least a college-level education). Before pregnancy, 18.5% of the women were underweight ($BMI < 18.5\,kg/m^2$), 68.3% were within the normal weight range (BMI between 18.5 and $23.9\,kg/m^2$), 11.4% were overweight (BMI between 24.0 and $27.9\,kg/m^2$), and only 1.9% were obese ($BMI \geq 28.0\,kg/m^2$). A total of 283 (33.5%) women were exposed to secondhand smoking during pregnancy,

and 439 (52.0%) women delivered boys (Table 1). The mean ± SD of birth weight was 3,319 ± 402g (range: 1,700 to 4,750g), of birth length was 50.2 ± 1.5 cm (range: 43.0 to 56.0 cm), and of ponderal index was 26.1 ± 2.1 kg/m^3 (range: 19.6 to 38.2 kg/m^3). In addition, 20 (2.4%) infants were born preterm and 83 (9.8%) infants were born small for gestational age (gestational age-adjusted SD-scores for birth weight <10th percentile).

The detection rate of BPA in all urine samples was 76.9% (1,950 samples), which was lower than that for BPF (98.3%, 2,492 samples) or BPS (86.8%, 2,200 samples). The median of BPA was 1.40 (IQR: 0.19–3.85) ng/mL in all urine samples, which was higher than for BPF (median = 0.65 ng/mL; IQR: 0.34–1.39 ng/mL) or BPS (median = 0.38 ng/mL; IQR: 0.13–1.11 ng/mL). Urinary concentrations of BPA, BPF, and BPS increased slightly during pregnancy (see Table S1) and were similar across different strata of covariates and some demographic and perinatal characteristics (Table 1). Urinary bisphenol concentrations of women included in the present study were compared with those of other populations from different countries in North America, Europe, and Asia (Table 2). Urinary BPA concentrations of the study population were generally lower than that of other populations, whereas urinary concentrations of BPF and BPS were similar or higher than those of other populations.

Urinary concentrations of BPA, BPF, and BPS were weakly correlated with each other, with Pearson correlation coefficients in each trimester between 0.10 and 0.31 (see Table S2). The ICC of urinary BPA concentrations throughout the whole pregnancy was 0.34 (95% CI: 0.30, 0.39), indicating a poor reproducibility during pregnancy. But both urinary concentrations of BPF [ICC = 0.57 (95% CI: 0.54, 0.61)] and BPS [ICC = 0.45 (95% CI: 0.41, 0.49)] had fair reproducibility during pregnancy. Similar ICCs of urinary bisphenol concentrations between each individual trimesters were also observed (see Table S3). Moreover, urinary SG of the study population had a low reliability [ICC = 0.18 (95% CI: 0.14, 0.23)] throughout the whole pregnancy, as well as between different trimesters.

After adjustment for potential confounders, urinary BPA concentrations in different trimesters were inversely, but not significantly, associated with birth weight and ponderal index, and urinary concentrations of BPF and BPS were inversely associated with birth weight, birth length, or ponderal index with some statistically significant findings (Figure 1). Each IQR increase in urinary BPF concentration in the first trimester was associated with reduced birth weight [$\beta = -27$ (95% CI: −55, 0 g)], and a significant reduction in ponderal index [$\beta = -0.17$ (95% CI: −0.32, −0.02 kg/m^3)] was associated with each IQR increase in urinary BPF concentrations in the third trimester. The associations were not significantly different across trimesters ($p_w > 0.1$). An IQR increase in urinary BPS concentrations in the first trimester was significantly associated with reduced birth weight [$\beta = -38$ (95% CI: −65, −11 g)] and ponderal index [$\beta = -0.18$ (95% CI: −0.34, −0.02 kg/m^3)], and the second-trimester concentrations of urinary BPS were significantly associated with reduced birth weight [$\beta = -43$ (95% CI: −71, −15 g)] and birth length [$\beta = -0.12$ (95% CI: −0.23, −0.02 cm)]. Notably, associations between urinary BPS concentrations and birth weight were significantly different across trimesters ($p_w = 0.01$) but not for birth length and ponderal index ($p_w > 0.1$). Associations for average concentrations of each bisphenol across the three trimesters were generally in the same direction as trimester-specific associations but were mostly nonsignificant. Mean birth weight, birth length, and ponderal index decreased across increasing quartiles of urinary concentrations of BPF and BPS in different trimesters, as did average concentrations (Figure 2; see also Table S4). In addition, after adjusting for other bisphenols, similar inverse associations of urinary concentrations of BPF and BPS with size at birth were observed, and these associations remained significant. Moreover, when additionally adjusting for pregnancy complications, the observed associations did not change when compared with those from the primary analysis (see Table S5).

Urinary bisphenol concentration patterns for women who delivered newborns in the 10th percentiles of birth weight, birth length, or ponderal index compared with those in the 90th percentiles are shown in Figure 3. For newborns in the 10th percentile of birth weight and birth length, maternal exposure levels of BPF and BPS were relatively higher than for newborns in the 90th percentile across the period of 10–36 weeks of gestation. In addition, mothers of newborns with a ponderal index in the 10th percentile had higher BPF concentrations across pregnancy but declining BPS concentrations across pregnancy. In addition, similar trends were observed in sensitivity analyses restricted to term deliveries (see Figure S1) and in sensitivity analyses restricted to women without pregnancy complications (see Figure S2).

In stratified analyses, we did not observe notable effect modifications by infant sex, parity, maternal age at recruitment, or maternal prepregnancy BMI ($p_{interaction} > 0.05$; see Table S6). The inverse associations between urinary bisphenol concentrations and birth weight were relatively more pronounced for boys, although the sex-based differences were not statistically significant ($p_{interaction} > 0.1$). Urinary BPA concentrations were inversely associated with ponderal index in nulliparous women and younger women (≤27 y of age), but were positively associated with ponderal index among multiparous women and older women (>27 y of age); the parity-based and age-based differences were marginally significant ($p_{interaction} < 0.1$). Moreover, results of sensitivity analyses restricted to term deliveries (see Table S7) or to women without pregnancy complications (see Table S8) did not change appreciably when compared with those of the primary analysis.

Discussion

In the present study, we examined and compared the trimester-specific associations of prenatal exposure to BPA, BPF, and BPS with size at birth in 845 women from a longitudinal prenatal cohort in Wuhan, China. We did not observe associations between urinary BPA concentrations during pregnancy and birth anthropometry. Instead, we observed that urinary concentrations of BPF and BPS in some trimesters were significantly associated with reduced birth weight, birth length, or ponderal index and that the associations were generally unchanged after additionally adjusting for other bisphenols. Moreover, newborns with smaller size at birth were born to women with relatively higher urinary concentrations of BPF and BPS during the course of pregnancy.

Urinary BPA concentrations in general populations have been decreasing since 2000 and 2014, whereas urinary concentrations of BPF and BPS have been increasing (Ye et al. 2015). In our participants, recruited between 2013 and 2015, the medians of urinary BPA concentrations were lower than in pregnant women from our previous study (Huo et al. 2015) or in a general population from Tianjin, China (Zhang et al. 2013). Urinary BPA concentrations of our participants were also relatively lower than preconception or pregnant women from different regions in the United States (Braun et al. 2012; Cantonwine et al. 2015; Hoepner et al. 2013; Meeker et al. 2013; Quiros-Alcalá et al. 2013), Spain (Casas et al. 2016; Valvi et al. 2013), Greece (Myridakis et al. 2015), France (Philippat et al. 2012), and the Netherlands (Jusko et al. 2014). It is noteworthy that most of those studies collected the urine samples between 1999 and 2012.

Table 1. Demographic and perinatal characteristics, and maternal urinary bisphenol concentrations [medians (25th–75th percentiles)] according to covariates of the study population from Wuhan, China (2013–2015).

		Bisphenol A (ng/mL)			Bisphenol F (ng/mL)			Bisphenol S (ng/mL)		
Characteristics	*n* (%) or mean ± SD	1st trimester	2nd trimester	3rd trimester	1st trimester	2nd trimester	3rd trimester	1st trimester	2nd trimester	3rd trimester
All participants	845 (100)	1.3 (0.1–3.4)	1.5 (0.2–3.8)	1.5 (0.3–4.4)	0.6 (0.3–1.3)	0.7 (0.4–1.4)	0.7 (0.4–1.5)	0.3 (0.1–1.0)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
Maternal age at recruitment (y)										
<25	105 (12.4)	1.1 (0.03–4.3)	1.4 (0.03–4.4)	1.6 (0.03–6.8)	0.5 (0.3–1.0)	0.6 (0.3–1.3)	0.7 (0.4–1.4)	0.3 (0.1–0.8)	0.4 (0.2–0.9)	0.4 (0.2–1.4)
25–30	517 (61.2)	1.2 (0.03–3.2)	1.4 (0.03–3.6)	1.5 (0.3–4.1)	0.6 (0.3–1.4)	0.7 (0.4–1.4)	0.7 (0.4–1.5)	0.3 (0.1–0.9)	0.4 (0.1–1.1)	0.4 (0.2–1.1)
30–35	182 (21.5)	1.6 (0.3–3.9)	1.7 (0.5–3.7)	1.4 (0.3–4.8)	0.6 (0.3–1.4)	0.7 (0.3–1.3)	0.7 (0.3–1.5)	0.4 (0.1–1.0)	0.4 (0.2–1.4)	0.5 (0.2–1.2)
≥35	41 (4.9)	1.0 (0.2–3.6)	1.7 (0.6–4.6)	1.8 (0.6–3.4)	0.5 (0.4–1.2)	0.8 (0.4–1.3)	0.6 (0.5–1.2)	0.2 (0.1–1.6)	0.5 (0.2–1.3)	0.5 (0.2–1.5)
Maternal height (cm)	161 ± 4	—	—	—	—	—	—	—	—	—
Maternal BMI before pregnancy BMI (kg/m^2)										
<18.5	156 (18.5)	1.1 (0.03–2.6)	1.1 (0.03–2.6)	1.8 (0.4–4.0)	0.6 (0.2–1.0)	0.7 (0.3–1.3)	0.8 (0.4–1.5)	0.2 (0.1–0.8)	0.3 (0.1–0.9)	0.5 (0.2–1.3)
18.5–23.9	577 (68.3)	1.4 (0.1–3.8)	1.5 (0.3–4.2)	1.5 (0.3–4.5)	0.6 (0.3–1.4)	0.7 (0.4–1.3)	0.7 (0.4–1.5)	0.3 (0.1–0.9)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
24.0–27.9	96 (11.4)	1.1 (0.1–3.5)	1.4 (0.03–3.1)	1.3 (0.1–4.6)	0.6 (0.3–1.9)	0.8 (0.4–2.0)	0.6 (0.3–1.3)	0.3 (0.2–1.6)	0.6 (0.2–1.4)	0.4 (0.2–1.0)
≥28.0	16 (1.9)	1.2 (0.03–2.4)	1.9 (0.5–4.7)	1.7 (0.1–2.7)	0.7 (0.2–1.2)	0.6 (0.2–1.3)	0.6 (0.2–1.7)	0.4 (0.1–0.9)	0.3 (0.1–0.5)	0.2 (0.1–0.9)
Parity										
Nulliparous	726 (85.9)	1.2 (0.1–3.4)	1.4 (0.1–3.8)	1.6 (0.3–4.5)	0.6 (0.3–1.3)	0.7 (0.4–1.4)	0.7 (0.4–1.5)	0.3 (0.1–0.9)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
Multiparous	119 (14.1)	1.5 (0.1–3.6)	1.6 (0.4–3.8)	1.2 (0.3–3.6)	0.6 (0.3–1.7)	0.6 (0.3–1.3)	0.7 (0.3–1.3)	0.3 (0.1–1.4)	0.4 (0.2–1.2)	0.3 (0.1–0.8)
Hypertensive disorders in pregnancy										
No	823 (97.4)	1.3 (0.1–3.5)	1.5 (0.1–3.8)	1.5 (0.3–4.4)	0.6 (0.3–1.3)	0.7 (0.4–1.4)	0.7 (0.4–1.5)	0.3 (0.1–1.0)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
Hypertension	18 (2.1)	0.7 (0.03–2.0)	1.4 (0.3–4.6)	1.5 (0.1–7.8)	0.5 (0.2–1.0)	1.0 (0.2–2.3)	0.5 (0.2–0.7)	0.3 (0.1–0.8)	0.7 (0.4–1.9)	0.5 (0.2–1.2)
Preeclampsia	4 (0.5)	0.8 (0.2–2.3)	2.0 (1.0–4.0)	2.4 (1.5–8.9)	0.6 (0.4–3.0)	0.5 (0.2–11)	0.8 (0.3–3.3)	0.3 (0.2–0.4)	0.3 (0.3–0.7)	0.3 (0.1–1.7)
Gestational diabetes mellitus										
No	769 (91.0)	1.2 (0.05–3.4)	1.4 (0.1–3.8)	1.5 (0.3–4.5)	0.6 (0.3–1.3)	0.7 (0.3–1.3)	0.7 (0.4–1.4)	0.3 (0.1–0.9)	0.4 (0.1–1.1)	0.4 (0.2–1.2)
Yes	76 (9.0)	1.4 (0.3–3.7)	1.5 (0.3–4.1)	1.1 (0.3–3.2)	0.6 (0.4–1.9)	0.8 (0.4–1.8)	0.8 (0.4–2.2)	0.3 (0.1–1.2)	0.5 (0.1–1.3)	0.5 (0.2–1.5)
Maternal anemia during pregnancy										
No	813 (96.2)	1.3 (0.1–3.4)	1.4 (0.2–3.8)	1.5 (0.3–4.5)	0.6 (0.3–1.3)	0.7 (0.4–1.4)	0.7 (0.4–1.5)	0.3 (0.1–1.0)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
Yes	32 (3.8)	1.3 (0.2–3.5)	1.9 (0.03–4.2)	1.4 (0.6–3.2)	0.4 (0.3–0.7)	0.7 (0.3–1.4)	0.5 (0.3–1.6)	0.1 (0.1–0.3)	0.2 (0.05–0.5)	0.3 (0.1–0.7)
Maternal pregnancy complications[a]										
None	724 (85.7)	1.3 (0.1–3.4)	1.4 (0.1–3.8)	1.5 (0.3–4.5)	0.6 (0.3–1.3)	0.7 (0.4–1.3)	0.7 (0.4–1.4)	0.3 (0.1–1.0)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
At least one	121 (14.3)	1.3 (0.2–3.4)	1.5 (0.3–3.8)	1.3 (0.4–3.4)	0.6 (0.3–1.5)	0.8 (0.3–1.9)	0.6 (0.3–1.8)	0.2 (0.1–0.9)	0.5 (0.1–1.1)	0.4 (0.2–1.1)
Maternal passive smoking during pregnancy										
No	562 (66.5)	1.2 (0.03–3.4)	1.4 (0.2–3.8)	1.5 (0.3–4.2)	0.6 (0.3–1.4)	0.7 (0.4–1.4)	0.7 (0.4–1.5)	0.3 (0.1–1.0)	0.4 (0.1–1.3)	0.4 (0.2–1.2)
Yes	283 (33.5)	1.3 (0.3–3.5)	1.5 (0.2–3.8)	1.5 (0.3–4.8)	0.6 (0.3–1.3)	0.6 (0.3–1.3)	0.7 (0.3–1.5)	0.3 (0.1–0.9)	0.4 (0.1–0.9)	0.4 (0.2–1.2)
Maternal education (y)										
≤9	50 (5.9)	1.2 (0.03–2.8)	1.4 (0.3–3.8)	1.2 (0.2–3.9)	0.7 (0.4–1.3)	0.8 (0.4–1.3)	0.7 (0.4–1.5)	0.3 (0.2–1.2)	0.5 (0.3–1.7)	0.5 (0.2–2.3)
9–12	128 (15.1)	1.3 (0.4–3.8)	1.3 (0.2–3.8)	1.6 (0.4–4.1)	0.6 (0.3–1.2)	0.7 (0.3–1.2)	0.7 (0.4–1.5)	0.3 (0.1–0.8)	0.3 (0.1–1.0)	0.4 (0.2–1.0)
>12	667 (78.9)	1.2 (0.03–3.4)	1.5 (0.1–3.8)	1.5 (0.3–4.5)	0.6 (0.3–1.4)	0.7 (0.4–1.4)	0.7 (0.3–1.5)	0.3 (0.1–1.0)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
Maternal folic acid supplementation during pregnancy										
No	196 (23.2)	1.2 (0.1–3.3)	1.4 (0.2–4.1)	1.7 (0.4–6.2)	0.6 (0.3–1.1)	0.8 (0.4–1.4)	0.7 (0.4–1.7)	0.3 (0.1–0.9)	0.4 (0.2–1.0)	0.5 (0.2–1.3)
1st trimester only	295 (34.9)	1.3 (0.1–3.7)	1.5 (0.2–3.9)	1.6 (0.3–4.2)	0.6 (0.3–1.5)	0.6 (0.3–1.3)	0.7 (0.3–1.3)	0.3 (0.1–1.1)	0.4 (0.1–1.3)	0.4 (0.2–1.1)
2nd and 3rd trimesters	139 (16.4)	1.0 (0.1–2.9)	1.5 (0.03–3.8)	1.2 (0.03–3.8)	0.6 (0.3–1.2)	0.6 (0.3–1.4)	0.6 (0.4–1.5)	0.3 (0.1–0.8)	0.3 (0.1–1.2)	0.4 (0.2–1.3)
Entire pregnancy	215 (25.4)	1.4 (0.03–3.5)	1.3 (0.03–3.2)	1.4 (0.2–3.5)	0.6 (0.3–1.4)	0.7 (0.4–1.3)	0.8 (0.4–1.6)	0.3 (0.1–1.1)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
Paternal height (cm)	174 ± 5	—	—	—	—	—	—	—	—	—
Infant sex										
Male	439 (52.0)	1.2 (0.05–3.4)	1.4 (0.1–3.9)	1.5 (0.2–4.2)	0.6 (0.3–1.4)	0.7 (0.4–1.3)	0.7 (0.4–1.3)	0.3 (0.1–1.0)	0.4 (0.2–1.3)	0.5 (0.2–1.2)
Female	406 (48.0)	1.3 (0.1–3.5)	1.5 (0.2–3.6)	1.5 (0.3–4.5)	0.6 (0.3–1.3)	0.7 (0.3–1.4)	0.7 (0.3–1.6)	0.3 (0.1–0.8)	0.4 (0.1–1.1)	0.4 (0.1–1.2)
Preterm delivery										
No	825 (97.6)	1.2 (0.1–3.4)	1.4 (0.1–3.8)	1.5 (0.3–4.2)	0.6 (0.3–1.3)	0.7 (0.4–1.4)	0.7 (0.4–1.5)	0.3 (0.1–0.9)	0.4 (0.1–1.2)	0.4 (0.2–1.2)
Yes	20 (2.4)	3.0 (1.0–5.6)	2.9 (1.8–6.8)	3.0 (0.9–6.9)	0.6 (0.3–1.4)	0.5 (0.3–1.0)	0.4 (0.2–0.7)	0.5 (0.1–1.4)	0.4 (0.2–1.3)	0.3 (0.1–0.8)

Note: Data are complete for all variables shown. —, Not applicable; BMI, body mass index; SD, standard deviation.

[a]Pregnancy complications include hypertensive disorders in pregnancy, gestational diabetes mellitus, and anemia during pregnancy.

Table 2. Urinary concentration comparisons.

Study	Location	Sample years	n	Samples	Value	Urinary bisphenol concentrations (ng/mL) Bisphenol A	Bisphenol F	Bisphenol S
Preconception or pregnant women								
Present study	Wuhan, China	2013–2015	845	T1 (13.0 weeks)	Med (25–75th)[a]	1.3 (0.1–3.4)	0.6 (0.3–1.3)	0.3 (0.1–1.0)
					GM (95% CI)	0.8 (0.7, 0.9)	0.6 (0.6, 0.7)	0.3 (0.3, 0.4)
			845	T2 (23.6 weeks)	Med (25–75th)[a]	1.5 (0.2–3.8)	0.7 (0.4–1.4)	0.4 (0.1–1.2)
					GM (95% CI)	0.9 (0.7, 1.0)	0.7 (0.6, 0.8)	0.4 (0.4, 0.4)
			845	T3 (36.0 weeks)	Med (25–75th)[a]	1.5 (0.3–4.4)	0.7 (0.4–1.5)	0.4 (0.2–1.2)
					GM (95% CI)	1.0 (0.8, 1.1)	0.7 (0.7, 0.8)	0.5 (0.4, 0.5)
			2,535	All samples	Med (25–75th)[a]	1.4 (0.2–3.9)	0.7 (0.3–1.4)	0.4 (0.1–1.1)
					GM (95% CI)	0.9 (0.8, 0.9)	0.7 (0.7, 0.7)	0.4 (0.4, 0.4)
					ICC (95% CI)[b]	0.34 (0.30, 0.39)	0.57 (0.54, 0.61)	0.45 (0.41, 0.49)
Quiros-Alcalá et al. 2013 (CHAMACOS)	USA	1999–2000	407	T1 (14 weeks)	GM (GSD)	0.9 (2.8)	—	—
					GM (GSD)[a]	1.2 (2.4)	—	—
			459	T2 (26 weeks)	GM (GSD)	1.0 (2.6)	—	—
					GM (GSD)[a]	1.2 (2.2)	—	—
					ICC	0.22	—	—
					ICC[b]	0.16	—	—
Hoepner et al. 2013 (CCCEH)	USA	1999–2006	375	T3 (34.7 weeks)	GM (95% CI)	1.8 (1.7, 2.0)	—	—
Philippat et al. 2012	French[c]	2002–2006	191	6–30 weeks[c]	Med (5–95th)	3.1 (0.8–10)	—	—
Jusko et al. 2014 (Generation R)	the Netherlands	2002–2006	80	<18 weeks	Med (25–75th)	1.1 (0.6–3.3)	—	—
			80	18–25 weeks	Med (25–75th)	1.5 (0.6–3.2)	—	—
			80	>25 weeks	Med (25–75th)	1.6 (0.8–2.6)	—	—
					ICC (95% CI)	0.32 (0.18–0.46)	—	—
Braun et al. 2012 (EARTH)	USA	2004–2009	137	Preconception	Med (25–75th)[a]	1.5 (1.1–2.1)	—	—
					ICC[b]	0.27	—	—
			137	During pregnancy	Med (25–75th)[a]	1.5 (1.1–2.3)	—	—
					ICC[b]	0.37	—	—
Casas et al. 2016 (INMA–Sabadell)	Spain	2004–2006	470	T1 and T3	GM (95% CI)	2.3 (2.1, 2.4)	—	—
					ICC (95% CI)	0.15 (0.06, 0.24)	—	—
Valvi et al. 2013 (INMA–Sabadell)	Spain	2004–2006	402	T1 (12 weeks)	Med (25–75th)	2.0 (1.2–3.6)	—	—
				T3 (32 weeks)	Med (25–75th)	1.8 (1.0–3.2)	—	—
				Average	Med (25–75th)	2.2 (1.4–3.6)	—	—
Braun et al. 2017 (MIREC)	Canada	2005–2009	812	T1 (12 weeks)	Med (25–75th)[a]	0.8 (0.1–1.5)	—	—
Smarr et al. 2015	USA	2005–2009	213	Preconception	GM (95% CI)	0.4 (0.3, 0.5)	—	—
					ICC (95% CI)	0.38 (0.31–0.45)	—	—
Cantonwine et al. 2015	USA	2006–2008	351	Visit 1 (9.7 weeks)	GM (GSD)[a]	1.3 (2.3)	—	—
			304	Visit 2 (17.9 weeks)	GM (GSD)[a]	1.3 (2.1)	—	—
			301	Visit 3 (26.0 weeks)	GM (GSD)[a]	1.4 (2.3)	—	—
			314	Visit 4 (35.1 weeks)	GM (GSD)[a]	1.3 (2.2)	—	—
					ICC (95% CI)[b]	0.19 (0.14, 0.26)	—	—
Ferguson et al. 2018 (LIFECODES)	USA	2006–2008	476	T1, T2, and T3	Med (25–75th)[a]	—	—	<0.4 (<0.4 – 0.6)
Myridakis et al. 2015 (Rhea)	Greece	2007–2008	239	T1 (10–13 weeks)	GM (95% CI)	1.2 (1.1, 1.4)	—	—
Meeker et al. 2013 (PROTECT)	Puerto Rico	2010–2012	105	During pregnancy	GM (95% CI)[a]	2.6 (2.3, 2.9)	—	—
					ICC (95% CI)[b]	0.24 (0.13, 0.40)	—	—
Huo et al. 2015 (HBC)	Wuhan, China	2012–2014	339[d]	Before delivery	GM (95% CI)	2.1 (1.7, 2.5)	—	—
Wan et al. 2018 (HBC)	Wuhan, China	2012–2014	985	Before delivery	GM (25–75th)	—	—	0.2 (0.1–0.4)
					GM (25–75th)[a]	—	—	0.2 (0.1–0.4)
General population								
Zhang et al. 2013	Tianjin, China	2010	50	Men and women	Med (range)	1.6 (<0.1 – 8.7)	—	—
			23	Women	Med (range)	1.7 (<0.1 – 8.7)	—	—
Liu et al. 2017 (NHANES)	USA	2013–2014	1,521	Men and women	Med (25–75th)	1.3 (0.6–2.5)	0.3 (0.1–1.1)	0.4 (0.1–0.9)
Ye et al. 2015 (NHANES)	USA	2014	42	Men and women	GM (95% CI)	0.4 (<0.1, 5.2)	0.4 (0.3, 0.6)	0.3 (<0.1, 3.1)
Zhang et al. 2016	Longtang Town, China	2014	116	Adults in e-waste area	Med (range)	3.0 (0.2–27.6)	0.4 (<0.1 – 8.7)	0.4 (<0.1 – 1.4)
Zhang et al. 2016	Qingyuan City, China	2014	22	Adults in rural area	Med (range)	0.6 (<0.1 – 4.1)	0.1 (<0.1 – 0.9)	0.4 (0.2–1.1)
			20	Adults in urban area	Med (range)	1.4 (<0.1 – 4.1)	0.5 (0.1–3.0)	0.8 (0.1–1.6)

Note: —, Not applicable; CCCEH, Columbia Center for Children's Environmental Health; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; EARTH, Environment and Reproductive Health Study; GM, geometric mean; GSD, geometric standard deviation; HBC, Healthy Baby Cohort; ICC, intraclass coefficient; INMA-Sabadell, INfancia y Medio Ambiente study in Sabadell, Spain; LIFECODES, the LifeCodes Cohort in Boston, Massachusetts; Med, median; MIREC, Maternal-Infant Research on Environmental Chemicals; NHANES, National Health and Nutrition Examination Survey; PROTECT, Puerto Rico Testsite for Exploring Contamination Threats; Rhea, the mother–child cohort study in Crete; SG, specific gravity; T, trimester.

[a]SG-adjusted urinary bisphenol concentration (ng/mL).

[b]ICCs and/or 95% CIs for SG-adjusted urinary bisphenol A concentrations.

[c]The study population was from two French birth cohorts: EDEN (Etude des Déterminants pré et post natals du développement et de la santé de l'Enfant) and PELAGIE (Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance) mother–child cohorts. Urinary samples were collected at 6–19 weeks (PELAGIE) and 24–30 weeks (EDEN).

[d]Urinary bisphenol A concentrations of controls for the nested case–control study.

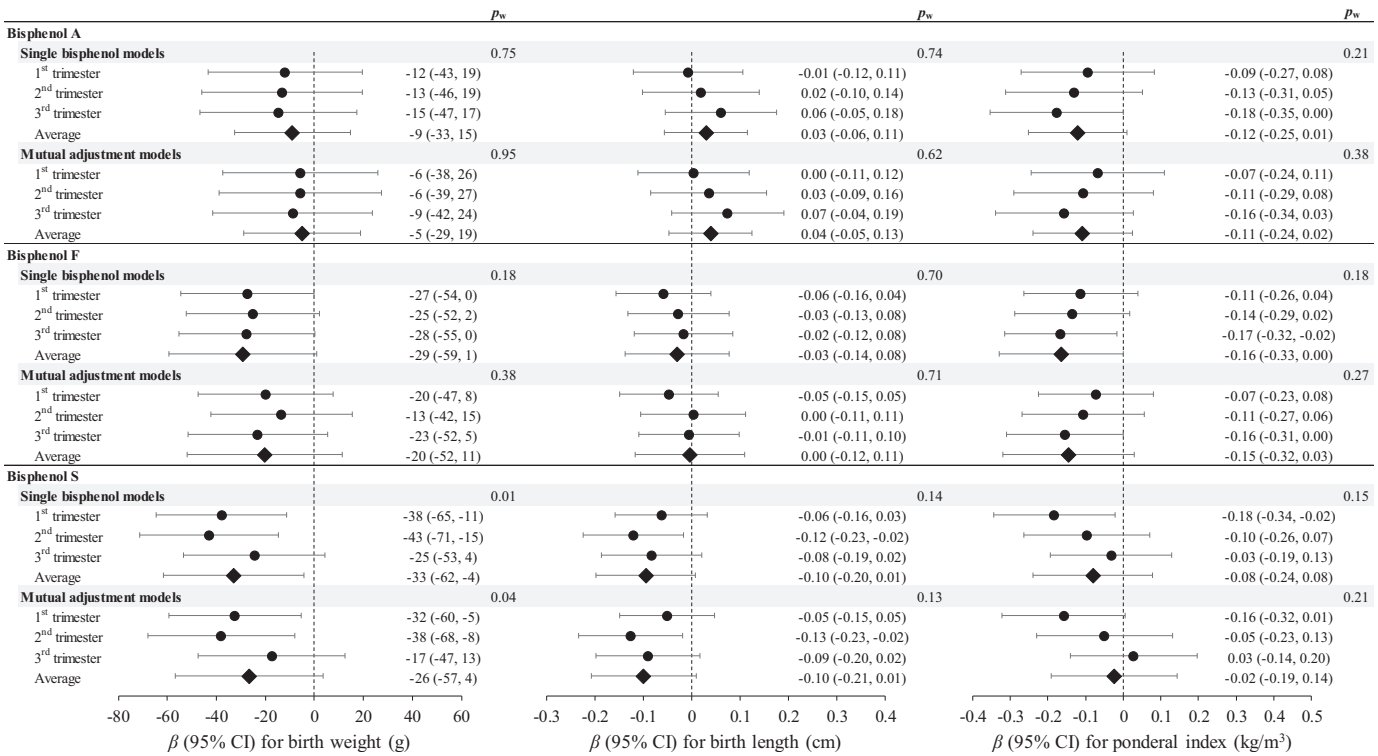

Figure 1. Associations between urinary bisphenol concentrations (per interquartile range increase) and size at birth. Regression coefficients (βs) and 95% confidence intervals (CIs) for trimester-specific associations of urinary concentrations of bisphenol A (BPA), bisphenol F (BPF), and bisphenol S (BPS) (per interquartile range) with original values of birth weight (in grams), birth length (in centimeters), and ponderal index (in kilograms per cubic meter) were estimated using multiple informant models. Associations between average concentrations of each bisphenol across the three trimesters were estimated using linear regression models. The single bisphenol models were adjusted for gestational age at delivery, maternal age at recruitment, parity, prepregnancy body mass index, passive smoking during pregnancy, education, folic acid supplementation, infant sex, and maternal and paternal height (only in birth length models). The mutual adjustment models were adjusted for variables in the single bisphenol models and mutually adjusted for urinary concentrations of BPA, BPF, and BPS. Trimester-specific interquartile ranges for BPA, BPF, and BPS are provided in Table S1. $p_w < 0.05$ indicates that associations were statistically different across trimesters.

Urinary BPA concentrations of women from a 10-city Canadian birth cohort, carried out between 2008 and 2011, were similar to that of our participants (Braun et al. 2017). To our knowledge, only a study of Michigan and Texas women who were trying to conceive, conducted between 2005 and 2009, reported a urinary BPA concentration [geometric mean = 0.38 (95% CI: 0.31, 0.45) ng/mL] lower than the present study (Smarr et al. 2015). Furthermore, urinary concentrations of BPF and BPS for women in the present study were similar to or higher than those in general populations sampled between 2009 and 2015 from urban China (Zhang et al. 2016) and the United States (Liu et al. 2017; Ye et al. 2015). No studies have reported urinary BPF concentrations in pregnant women. Only two recent studies reported urinary BPS concentrations during pregnancy that were lower than in the women in the present study. One of those two studies was carried out in the United States between 2006 and 2008 (Ferguson et al. 2018) and the other was one of our previous studies conducted between 2012 and 2014 (Wan et al. 2018). Based on the comparisons, we could conclude a downward trend for urinary BPA concentrations and upward trends for urinary concentrations of BPF and BPS across time at population levels. A potential explanation could be the widespread use of BPA-free products in recent years. In addition, our participants had relatively higher education levels, and they might intentionally avoid using products containing BPA before and during pregnancy.

Urinary BPA concentrations of the study population indicated poor reproducibility during pregnancy, which was consistent with previous studies (Braun et al. 2011, 2012; Cantonwine et al. 2015; Casas et al. 2016; Jusko et al. 2014). The poor reproducibility during pregnancy might be a result of the short half-life (∼6 h) of BPA excreted from the human body (Dekant and Völkel 2008). Similarly, the half-life of BPS excreted from the human body is <7 h (Oh et al. 2018). We are unaware of any studies estimating the half-life of BPF. Moreover, we are not aware of any studies reporting the reproducibility of urinary concentrations of BPF and BPS during pregnancy. In the present study, we observed fair reproducibility for urinary concentrations of BPF and BPS, suggesting that BPF and BPS could have been used in additional products rather than only being used as BPA replacements. Future studies could investigate the exposure sources of BPF and BPS for humans, as well as other BPA substitutes.

Prenatal exposure to BPA in ewes at environmentally relevant doses was associated with reduced body weight in their offspring (Savabieasfahani et al. 2006). However, the impact of prenatal exposure to BPA on size at birth is not clearly understood because of the inconsistent findings from current epidemiological studies (Pergialiotis et al. 2018). In a nested case–control study of low birth weight (birth weight <2,500 g; 113 cases and 339 matched controls), urinary BPA concentrations in the third trimester were associated with increased risk of low birth weight (Huo et al. 2015). A prospective cohort study from the Netherlands reported that higher urinary BPA concentrations during pregnancy were associated with reduced fetal weight, measured by ultrasound, and birth weight (Snijder et al. 2013). Another nested case–control study, from the United States, related urinary BPA concentrations

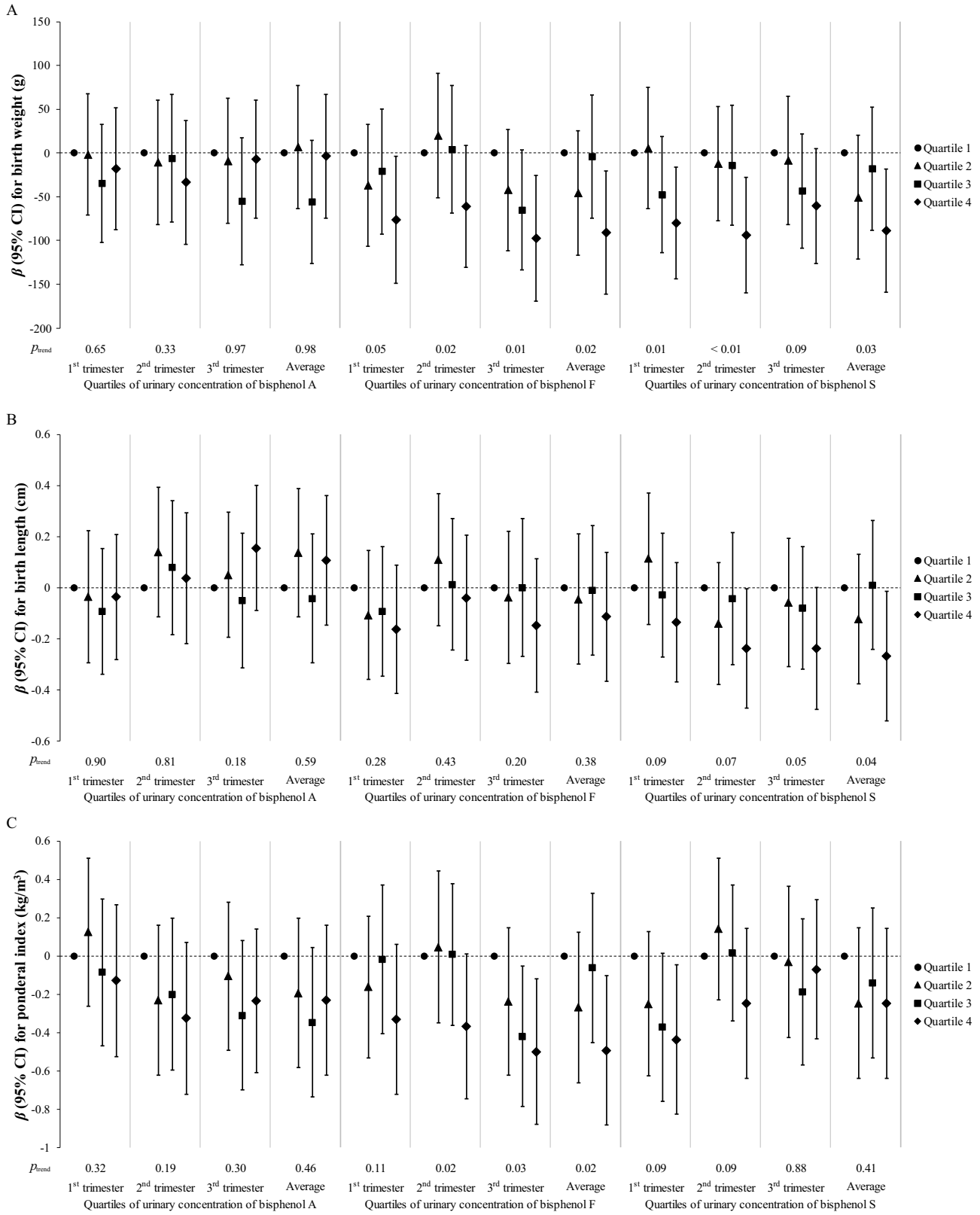

Figure 2. Associations between quartiles of urinary bisphenol concentrations and size at birth. Regression coefficients (βs) and 95% confidence intervals (CIs) for associations of trimester-specific quartiles of urinary concentrations of bisphenol A, bisphenol F, and bisphenol S with original values of birth weight (in grams), birth length (in centimeters) and ponderal index (in kilograms per cubic meter) were estimated using multiple informant models. Associations between quartiles of average concentrations of each bisphenol across the three trimesters were estimated using linear regression models. All models were adjusted for gestational age at delivery, maternal age at recruitment, parity, prepregnancy body mass index, passive smoking during pregnancy, education, folic acid supplementation, and infant sex. Birth length models were additionally adjusted for maternal and paternal height. Numeric data are available in Table S4.

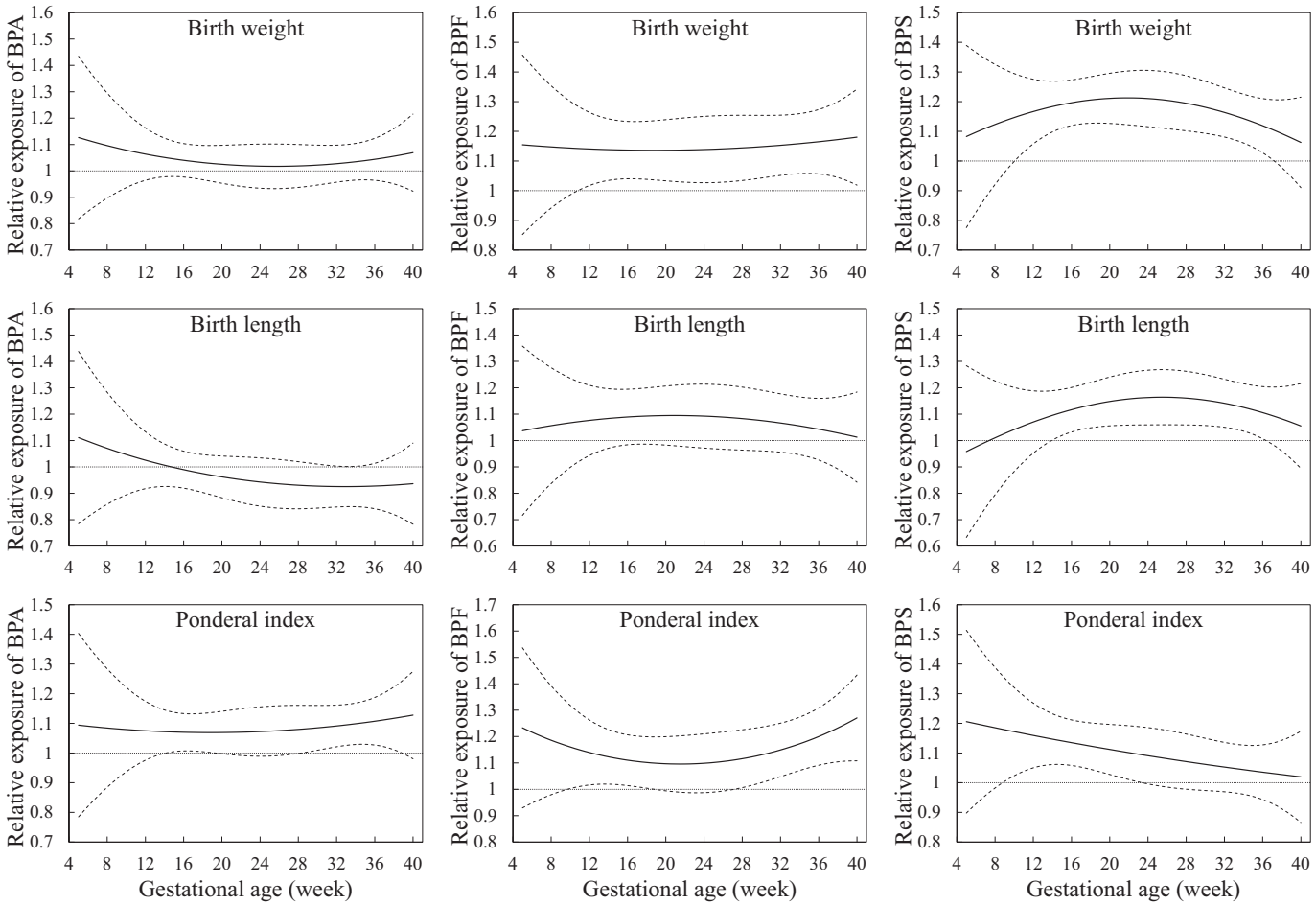

Figure 3. Relative exposure of bisphenols comparing newborns in the 10th percentile of birth weight, birth length, or ponderal index to those in the 90th percentile. Solid lines represent relative exposures of bisphenol A, bisphenol F, or bisphenol S in the 10th percentile of birth weight, birth length, or ponderal index to those in the 90th percentiles. Dotted lines represent pointwise 95% confidence intervals. All models were adjusted for maternal age at recruitment, parity, prepregnancy body mass index, passive smoking during pregnancy, hypertensive disorders of pregnancy, gestational diabetes mellitus, education, and infant sex. Models for birth length were additionally adjusted for maternal and paternal height.

during pregnancy with increased risk of preterm delivery (Cantonwine et al. 2015). On the contrary, a study from South Korea reported a positive association of urinary BPA concentrations in the third trimester with birth weight (Lee et al. 2014). A French cohort also revealed positive associations of BPA exposure during pregnancy and head circumference at birth (Philippat et al. 2012). However, the present study and studies from the United States (Ferguson et al. 2016; Smarr et al. 2015) and Spain (Casas et al. 2016) did not support associations of BPA exposures before and during pregnancy with fetal growth. Therefore, more studies are needed to investigate the effect of exposure to BPA during pregnancy on fetal growth in humans.

To our knowledge, no epidemiological studies have estimated the relationship between BPF exposure during pregnancy and fetal growth, but there were two studies for BPS. One study, from our research team, reported that urinary BPS concentration in the third trimester was significantly associated with increased pregnancy duration, but BPS was not significantly associated with reduced birth weight (Wan et al. 2018); urine samples in the first and second trimesters were not available. The other study was conducted in the United States and suggested inverse associations between urinary BPS concentrations during pregnancy, at up to three time points, and birth weight in boys (Ferguson et al. 2018). In the present study, the observed inverse associations of urinary concentrations of BPF and BPS with birth weight were also relatively more pronounced in boys, but the sex-based difference was not significant. Future studies with larger sample sizes are needed to investigate whether there are sex-specific effects of BPF and BPS on size at birth.

Fetuses are more sensitive to environmental exposures than adults (Braun 2017). Identifying critical windows of susceptibility to environmental pollutant exposures during pregnancy is particularly crucial for researching infants' and children's health (Sánchez et al. 2011). Prenatal exposure to bisphenols during critical windows of susceptibility could have larger effects, compared with exposures during other time periods, on fetal growth (Barr et al. 2000; Sánchez et al. 2011). In the present study, using multiple informant models, we observed significantly different inverse associations between urinary BPS concentrations and birth weight across trimesters, suggesting relatively stronger associations for the exposure in first and second trimesters. But the multiple informant model is not robust to identify accurate windows of susceptibility (e.g., exposure at which exact weeks of gestational has stronger associations), and this approach is not able to account for variability in exposures within a given time window. We thus estimated exposure patterns during pregnancy by comparing newborns with low- versus high-gestational age-adjusted SD-scores. The results indicate that the exposure levels of BPF and BPS for newborns with restricted size at birth were

relatively higher throughout the whole pregnancy, especially between 10 and 36 weeks of gestation. Therefore, the whole pregnancy appears to be the critical window of susceptibility to BPF and BPS for fetal growth.

As manufacturers are switching to using BPF or BPS in their products instead of BPA (Bittner et al. 2014; Rochester and Bolden 2015), the amount of both bisphenols in everyday products could continue to increase. As a result, humans are exposed to BPF and BPS simultaneously through different sources. Our findings suggest that prenatal exposure to higher levels of BPF and BPS might be associated with reduced size at birth, and significant inverse associations were relatively more pronounced for birth weight and ponderal index. Ponderal index has been used as an indicator of asymmetrical intrauterine growth restriction (Landmann et al. 2006). The observed significant associations for ponderal index in our data were more likely to be driven by the associations for birth weight. Furthermore, exposure to bisphenols alters steroidogenesis in experimental animals and humans, and might affect fetal growth through multiple hormone-mediated mechanisms when exposed prenatally (Peretz et al. 2014; Rochester and Bolden 2015; Tomza-Marciniak et al. 2018). But the exact mechanisms underlying the inverse association between prenatal exposure to bisphenols and fetal growth remain unclear, especially for substitutes of BPA. Therefore, future studies are necessary to investigate the interaction effects of prenatal exposure to different bisphenols on fetal growth, as well as the underlying mechanisms.

One strength of the present study is the repeated measurements of urinary bisphenol concentrations. This enabled us to investigate the trimester-specific associations of bisphenol exposures with size at birth, as well as to estimate the critical windows of susceptibility to bisphenols. In addition, the present study had a large sample size of 845 women who provided urine samples in each of the first, second, and third trimesters, which provided enough power to investigate the associations between prenatal exposure to bisphenols and size at birth as well as to detect sex-specific effects. Finally, we measured urinary concentrations of BPA, BPF, and BPS using the state-of-the-art method and obtained accurate and reliable exposure assessments of these bisphenols, which also enabled us to mutually adjust for all three bisphenols.

A limitation of the present study is the potential for residual confounding from other environmental toxicants. Humans are simultaneously exposed to a large number of environmental pollutants, and many of those have been related with restricted fetal growth, including other endocrine-disrupting chemicals, persistent organic pollutants, heavy metals, and airborne pollutants (Zheng et al. 2016). Future studies investigating the impact of exposure to environmental chemical mixtures during pregnancy on fetal growth would help in understanding and controlling for this kind of residual confounding. Another limitation is that we did not systemically evaluate maternal diet during pregnancy, which might affect the fetal growth and also be a source of bisphenol exposures (Romano et al. 2014). Future studies are needed to investigate the impact of maternal diet and intrauterine nutritional conditions on the association of bisphenol exposures with fetal growth.

Conclusions

In this prospective prenatal cohort study, we observed significant inverse associations of urinary concentrations of BPF and BPS in some trimesters with birth weight, birth length, or ponderal index. But such inverse associations were not significant for BPA. We did not identify clear differences in associations according to trimester of exposure for BPF and BPS, suggesting that the entire gestational period may be a window of heightened susceptibility to these BPA replacements with regard their effects on fetal growth in humans. However, the observed associations in the present study need to be replicated in other populations, and sex-specific associations also need to be examined.

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